Measurement of Thyroxin Synthesis with I^{131}

A Test for Evaluation of Thyroid Function in Equivocal States

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• *As the function of the thyroid gland is the synthesis and secretion of thyroxin, a test which correctly measures this process is best for diagnosis of thyroid disorder and for determining the success of therapy. The rate of secretion can be measured with a Geiger counter which indicates what proportion of radioactive iodine in a serum specimen is in the form of thyroxin. The normal proportion is 2 to 10 per cent; in hyperthyroidism the proportion is 50 to 70 per cent, and in hypothyroidism less than 1 per cent.*

The same test has served to detect metastases of thyroid carcinoma following total thyroidectomy.

A CLASSICAL CASE of toxic goiter or of myxedema is not likely to require laboratory tests for diagnosis. Sufficient signs and symptoms are manifest in these states so that they are rarely overlooked by the physician. However, between these extremes of thyroid function there is a wide range of variation in activity of the gland, and within this range many cases of dysfunction are difficult to diagnose. Furthermore, hypermetabolic and hypometabolic disorders may be erroneously diagnosed as thyroid disease unless adequate laboratory studies are made. Laboratory procedures designed to aid in the correct diagnosis of thyroid disease are many, but few are simple enough for routine use and even fewer are sensitive enough for accuracy.

The test of basal metabolic rate as usually performed may give variable results. Particular attention must be given to the basal state of each patient, for even if conditions are ideal, diagnosis is often difficult in a given case because of the wide range of results in normal persons.[1, 2]

Determination of the amount of cholesterol in the blood has proved of little value in the diagnosis of hyperthyroid states, although it is of some value as a control measure in the treatment of hypothyroidism. For this test also there is a wide range of normal values, and the results are not specific for thyroid disease.[1, 9]

A similar criticism can be made even of the chemical determination of protein-bound iodine in the serum or plasma (Chart 1). Part of this lack of sensitivity may be attributable to the technical difficulties inherent in the analysis of extremely small amounts of iodine. In addition, conditions unrelated to thyroid abnormality such as pregnancy or nephrosis may cause results outside the normal range.[6, 10]

It has been suggested that the concentration of circulating thyroxin is the best measure of function of the thyroid gland. However, the level of concentration is a result and not the prime determinant of the rate of synthesis of thyroxin. It is the measurement of the actual speed of synthesis and secretion of thyroxin which should prove a more accurate indicator of glandular function. Further, there is evidence that the protein-bound iodine consists of not only the active hormone, thyroxin, but also organic iodine compounds of undetermined calorigenic activity.[4] Conditions increasing or decreasing the concentration of these other compounds in the blood could also contribute to the wide variation and overlap found in protein-bound iodine measurements.

Radioactive iodine has been widely used in recent years in the evaluation of thyroid function. With

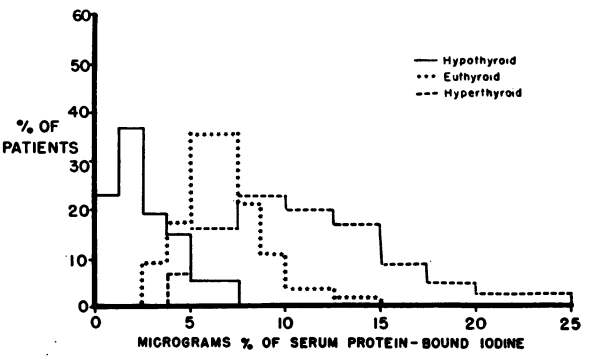

Chart 1. — Distribution of values for protein-bound iodine in the serum in 200 studies of patients with varying states of thyroid function. A significant degree of overlap can be observed.

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measurements of radioactive iodine, the limitations and variabilities of chemical methods of iodine analysis are avoided. Only emitted rays are measured. With the average Geiger counter less than a billionth of a microgram of radioiodine can be readily measured.

The measurement of the uptake of radioiodine by the thyroid gland over a period of 24 hours has been the most extensively used,[8] but results just as good have been obtained recently with one-hour uptake tests.[3, 5] However, difficulty is encountered in diagnosing cases even with uptake tests. The range of uptake in normal persons considerably overlaps the rates found in hypothyroid and hyperthyroid patients.[7] Chart 2, showing the distribution of uptake values observed in some 500 studies, indicates that the uptake of circulating iodide by the thyroid is not always a measure of thyroid hormone formation and secretion and therefore may not accurately depict overall thyroid function.

Thyroxin is stored in the follicles of the thyroid gland in the colloid protein, thyroglobulin. Under the influence of the thyrotropic hormone of the pituitary gland, thyroglobulin is hydrolysed and thyroxin is secreted as the amino acid into the blood. This process may be followed with radioactive iodine, which serves as a label of the endogenous circulating iodide, tracing its movement through the sequence of reactions which lead to the secretion of thyroxin from the thyroid into the bloodstream. The thyroxin synthesis test is a measure of the speed with which these processes take place. The results of the test are expressed as the percentage of radioactive iodine in the serum which is in the form of thyroxin.

Twenty-four hours after the oral administration of 100 microcuries of carrier-free radioiodine a specimen of blood is obtained. The serum is analyzed for total radioactive iodine and for radioactive iodine in the thyroxin form. The analysis is performed by first treating the serum with an alkaline reagent and then extracting the thyroxin with normal butanol.

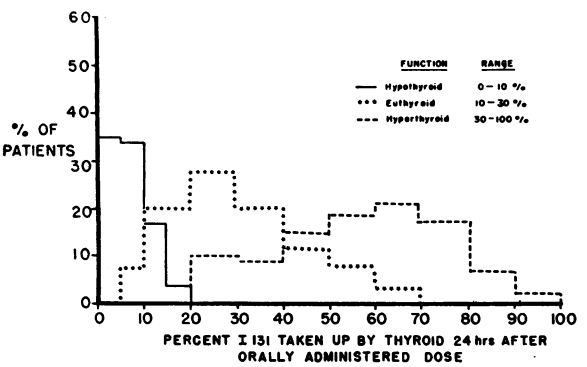

Chart 2.—Distribution of values for 24-hour thyroid gland uptake of radioactive iodine in 500 studies of patients with varying states of thyroid activity. Overlap is similar to that for protein-bound iodine.

The butanol extract is then washed with an alkaline reagent, which leaves the radioactive thyroxin in the alcohol layer. Only a 2 cc. sample of serum is necessary for the analysis. (Details will be published elsewhere.) As with other diagnostic techniques using radioiodine, previous intake of iodine-containing drugs can alter results.

The results in 500 studies of patients in the Veterans Administration Hospitals in Van Nuys and Long Beach are shown in Chart 3. Values in euthyroid persons range from 2 to 10 per cent; in most hyperthyroid persons the value is between 50 and 70 per cent; in nearly 95 per cent of hypothyroid persons it is less than 1 per cent, and the overlap between values found in euthyroid persons and those of patients with thyroid dysfunction is slight in comparison with the normal range. The diagnosis in all cases was based upon ultimate clinical outcome including therapeutic response in those with dysfunction. Each patient was first examined on the medical service, then referred to the metabolic ward of the radioisotope unit. After repeat examination, laboratory studies of thyroxin synthesis, of thyroid uptake and urinary excretion of radioiodine, of protein-bound iodine, and of blood cholesterol were made and the basal metabolic rate measured three times.

The sensitivity of the thyroxin synthesis test in indicating hypothyroidism and hyperthyroidism may be attributed, in part, to the fact that the turnover of circulating thyroxin rather than of a mixture of protein-bound iodine compounds is being measured. Chart 4 shows that the turnover of radioactive thyroxin differs from that of the non-thyroxin moiety of the radioactive protein-bound iodine,

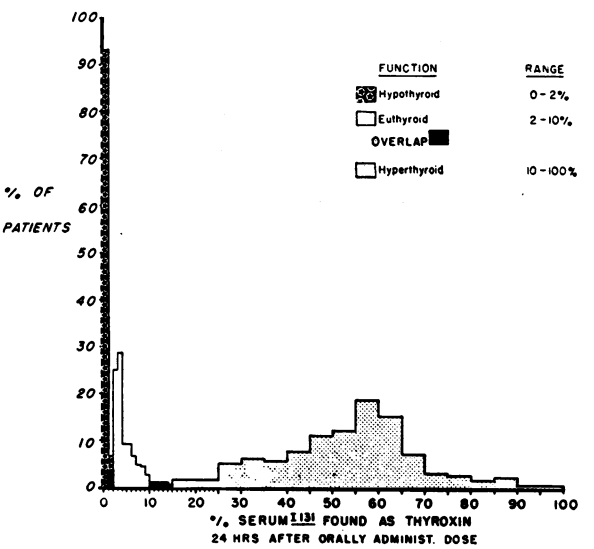

Chart 3.—Distribution of radiothyroxin synthesis values as found in 500 studies. There is relatively little overlap between different states of thyroid function.

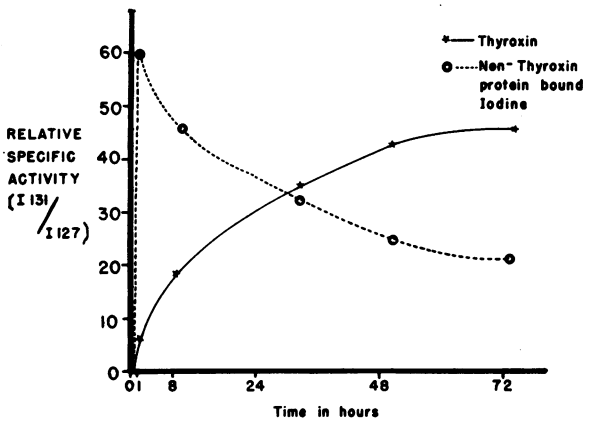

Chart 4.—The newly formed thyroxin, as measured with radioactive iodine, is shown to be different from the other organic iodine compounds in the protein-bound iodine of the serum in terms of its slower turnover rate.

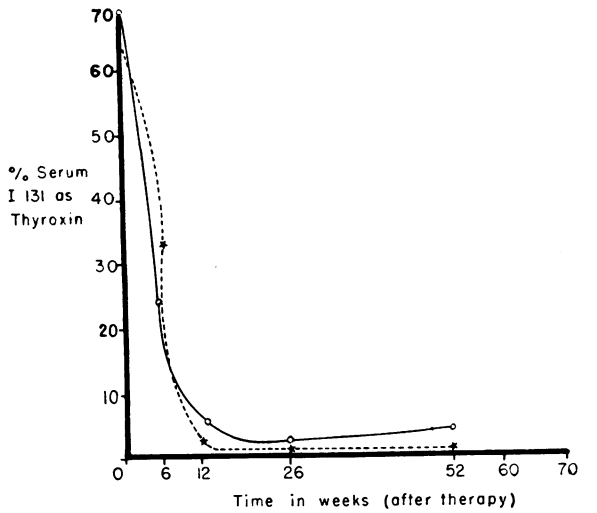

Chart 5.—Results of thyroxin synthesis determinations for two patients who received radioiodine for hyperthyroidism. The course of the patient traced by the solid line resulted in a euthyroid condition; that with the broken line depicts resultant hypothyroidism.

which appears to have a more rapid turnover than thyroxin.

Chart 5 shows thyroxin synthesis values in a patient treated with radioiodine for hyperthyroidism. Twenty-four hours after a test dose of I^{131}, 70 per cent of the radioiodine in the serum was in the form of thyroxin. On repeat test at the time of therapy a value of 69 per cent was obtained. Six weeks after the therapeutic dose the value was 24 per cent, indicating a definite therapeutic effect. At three months it was 6 per cent, and at six months 3 per cent. On follow-up one year after therapy a value of 4 per cent was obtained, still well within the euthyroid range. These results illustrate not only the separation between values found in hyperthyroidism and euthyroidism but also the constancy of the test as a measure of thyroid function and its usefulness in following the results of therapy. By testing at proper intervals the need for additional therapy can be anticipated and thus considerable time may be saved in restoring the patient to a euthyroid condition. The sensitivity of the test in distinguishing hypothyroidism from euthyroidism is also shown in Chart 5.

TABLE 1.—*Induction of Thyroxin Synthesis in Thyroid Carcinoma Metastases and Response to Radioiodine Therapy*

Time (months)	Cumulative I^{131} (mC)	24-Hour Thyroxin Synthesis (%)
0	0*	3.5
2	37	10.0
4	106	14.0
10	296	1.5
12	452	0.6
16	552	0.2

* One week before total thyroidectomy and radical neck dissection.

In another patient with hyperthyroidism treated with I^{131}, the thyroxin synthesis value was 63 per cent before treatment. Six weeks after therapy it was 32 per cent; after three months, 2 per cent; after six months, 0.4 per cent, and after one year, 0.5 per cent. At the end of a year the patient had symptoms and signs of myxedema, which responded to treatment with desiccated thyroid.

In Table 1 are shown results demonstrating the sensitivity of the thyroxin synthesis test in detecting functioning metastases of thyroid carcinoma following total thyroidectomy, radical neck dissection and repeated doses of radioactive iodine. The metastases were so small that they could not be delineated by scanning techniques. The intermediate rise in thyroxin synthesis values was attributed to thyrotropic hormone stimulation of the metastases.

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